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International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 :
C12N 15/12, C07K 14/47, C12Q 1/68, G01N 33/50, A61K 38/17, 48/00

A3

(11) International Publication Number: **WO 98/41631**

(43) International Publication Date: 24 September 1998 (24.09.98)

(21) International Application Number: PCT/US98/05506

(22) International Filing Date: 20 March 1998 (20.03.98)

(30) Priority Data:
08/821,355 20 March 1997 (20.03.97) US

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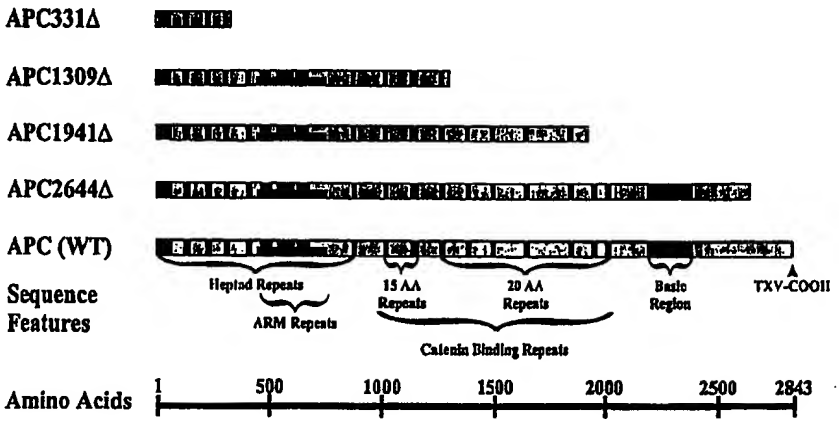
(81) Designated States: AU, CA, JP, European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).

Published
With international search report.
Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(88) Date of publication of the international search report:
3 December 1998 (03.12.98)

(54) Title: β-CATENIN, TCF-4, AND APC INTERACT TO PREVENT CANCER



(57) Abstract

The APC tumor suppressor protein binds to β-catenin, a protein recently shown to interact with Tcf/Lef transcription factors. Here, the gene encoding a Tcf family member that is expressed in colonic epithelium (*hTcf-4*) was cloned and characterized. hTcf-4 transactivates transcription only when associated with β-catenin. Nuclei of APC$^{-/-}$ colon carcinoma cells were found to contain a stable β-catenin-hTCF-4 complex that was constitutively active, as measured by transcription of a Tcf reporter gene. Reintroduction of APC removed β-catenin from hTcf4 and abrogated the transcriptional transactivation. Constitutive transcription of TCF target genes, caused by loss of APC function, may be a crucial event in the early transformation of colonic epithelium. It is also shown here that the products of mutant *APC* genes found in colorectal tumors are defective in regulating β-catenin/Tcf-4 transcriptional activation. Furthermore, colorectal tumors with intact *APC* genes were shown to contain subtle activating mutations of β-catenin that altered functionally significant phosphorylation sites. These results indicate that regulation of β-catenin is critical to APC's tumor suppressive effect and that this regulation can be circumvented by mutations in either APC or β-catenin.